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PRINCIPLES of INTERNAL MEDICINE

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The systemic nature of the disorder may cause confusion with other connective tissue diseases. The endocrine manifestations suggest an autoimmune basis of the disorder, but circulating antibodies against endocrine cells have not been demonstrated. Increased serum and tissue levels of interleukin 6 are present, but the pathophysiologic basis for the POEMS syndrome is uncertain. Therapy directed against the plasma cell dyscrasia such as local radiation of bony lesions or chemotherapy may result in endocrine improvement.

MISCELLANEOUS DISORDERS WITH ENDOCRINE MANIFESTATIONS

A variety of other clinical and genetic disorders are associated with multiple endocrine manifestations (Table 340-3). The molecular and genetic defects for several of these disorders are now known. One example is the McCune-Albright syndrome, in which a constitutively activating mutation of the α subunit of the stimulatory G-protein causes overactivity of adenylyl cyclase in a variety of glands. The clinical syndrome can include precocious puberty, acromegaly, thyrotoxicosis, and Cushing's syndrome, all reflecting autonomous hyperfunction of glands usually regulated by a G protein-dependent receptor.

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SECTION 2

DISORDERS OF INTERMEDIARY METABOLISM

341

Henry N. Ginsberg, Ira J. Goldberg

DISORDERS OF LIPOPROTEIN METABOLISM

Lipoproteins are macromolecular complexes that carry hydrophobic plasma lipids, particularly cholesterol and triglyceride, in the plasma. More than half of the coronary heart disease (CHD) in the United States is attributable to abnormalities in the levels and metabolism of plasma lipids and lipoproteins. Some premature CHD is due to mutations in major genes involved in lipoprotein metabolism, but elevated lipoprotein levels in most patients with CHD reflect the adverse impact of a sedentary lifestyle, excess body weight, and diets high in total and saturated fat on a less-than-perfect genetic background. Primary care providers and subspecialists need to understand the pathophysiology of and available therapies for these disorders. This chapter is focused on the major lipid disorders, both the dyslipoproteinemias caused by single-gene defects and the disorders that are likely to be polygenic in origin. We will then provide a practical approach to assist in the identification, evaluation, and treatment of patients with increased risk of CHD.

LIPID AND LIPOPROTEIN TRANSPORT

LIPOPROTEIN STRUCTURE Lipoproteins are spherical particles made up of hundreds of lipid and protein molecules. They are

smaller than red blood cells and visible only by electron microscopy. However, when the larger, triglyceride-rich lipoproteins are present in high concentration, plasma can appear turbid or milky to the naked eye. The major lipids of the lipoproteins are cholesterol, triglycerides, and phospholipids. Triglycerides and the esterified form of cholesterol (cholesteryl esters) are nonpolar lipids that are insoluble in aqueous environments (hydrophobic) and comprise the core of the lipoproteins. Phospholipids and a small quantity of free (unesterified) cholesterol, which are soluble in both lipid and aqueous environments (amphipathic), cover the surface of the particles, where they act as the interface between the plasma and core components. A family of proteins, the apolipoproteins, also occupies the surface of the lipoproteins to serve as an additional interface between lipid and aqueous environments. These proteins play crucial roles in the regulation of lipid transport and lipoprotein metabolism.

Lipoproteins have been classified on the basis of their densities into five major classes: chylomicrons, very low density lipoproteins (VLDL), intermediate-density lipoproteins (IDL), low-density lipoproteins (LDL), and high-density lipoproteins (HDL). The physical-chemical characteristics of the major lipoprotein classes are presented in Table 341-1.

APOLIPOPROTEINS The apolipoproteins (apos) provide structural stability to the lipoproteins and determine the metabolic fate of the particles upon which they reside. They were named in an arbitrary alphabetical order and, for the purposes of this discussion, will be described in relation to their association with lipoprotein classes (Table 341-2.)

and LDL, comprising approximately 60, 60, and 95 percent of the proteins in these lipoproteins respectively. Apo B100 has a molecular mass of about 545 kDa and is synthesized in the liver. It is essential for the assembly and secretion of VLDL from the liver and is the ligand for the removal of LDL by the LDL receptor. The LDL receptor is a cell-surface protein that binds and internalizes lipoproteins that contain apo B100 or apo E. The LDL receptor binding domain of apo B100 is the sequence between amino acids 3200 and 3600, a region that is absent in apo B48.

Apo B48 is essential for the assembly and secretion of chylomicrons. Apo B48 is encoded by the same gene and the same messenger ribonucleic acid (mRNA) as Apo B100, but in the intestine the mRNA is edited in an unusual way: A cytidine deaminase in the intestine changes a cytidine to a uridine in base 6666 of the apo B100 mRNA to produce a nonsense codon so that apo B48 contains only the N-terminal 48 percent of the full-length apo B100. In contrast, the apo B100 mRNA in human liver is not edited. The role of apo B48 in the metabolism of chylomicrons in plasma is unclear. Individuals with mutations that interfere with the normal synthesis of apo B have absent or very low levels of chylomicrons, VLDL, IDL and LDL.

The apolipoproteins of the C series are synthesized in the liver and are present in all plasma lipoproteins (trace amounts in LDL). Individual apo C's have different metabolic roles, but all inhibit the removal of plasma chylomicrons and VLDL remnants by the liver. Overexpression of apo C1 in transgenic mice inhibits the uptake of chylomicron and VLDL remnants by the liver. Apo C1 under- or overexpression has not been described in humans. Apo CII is an essential activator of the enzyme lipoprotein lipase (LPL), which hydrolyzes triglycerides in chylomicrons and VLDL, and individuals lacking apo CII have severe hypertriglyceridemia. Apo CIII inhibits LPL, and apo CIII overexpression in transgenic mice causes severe hypertriglyceridemia. Two humans who lacked apo CIII had accelerated rates of lipolysis of VLDL triglyceride.

Apo E is synthesized mainly in hepatocytes but is also made in other cells, including macrophages, neurons, and glial cells. It is found in chylomicrons, IDL, VLDL, and HDL and mediates the uptake of these lipoproteins in liver both by the LDL receptor and by the LDL receptor-related protein (LRP). Apo E can also bind to heparin-like proteoglycan molecules on the surface of all cells. Three major alleles of the apo E gene encode E2, E3, and E4, isoforms that differ in sequence at two positions and have frequencies of about 0.12, 0.75,

Lipoprotein	Density, g/dL	Molecular Mass, kDa	Diameter, nm	TG	Chol	PL
Chylomicrons	0.95	400×10^3	75-1200	80-95	2-7	3-9
VLDL	0.95-1.006	$10-80 \times 10^3$	30-80	55-80	5-15	10-20
IDL	1.006-1.019	$5-10 \times 10^3$	25-35	20-50	20-40	15-25
LDL	1.019-1.063	2.3×10^3	18-25	5-15	40-50	20-25
HDL	1.063-1.210	$1.7-3.6 \times 10^3$	5-12	5-10	15-25	20-30

NOTE: TG, triglyceride; Chol, the sum of free and esterified cholesterol; PL, phospholipid. The remaining percent composition is made up of the apoproteins.

and 0.13 in the general population. Apo E2 binds to the LDL receptor with lower affinity than apo E3 or E4. Individuals who are homozygous for apo E2 may develop severe hyperlipidemia (type III dyslipoproteinemia), and complete absence of apo E causes elevations of plasma levels of chylomicron and VLDL remnants and early atherosclerosis.

Apo AI, apo AII, and apo AIV are found primarily on HDL. Apo AI and apo AII are synthesized in the small intestine and the liver; apo AIV is made only in the intestine. Apo AI comprises about 70 to 80 percent of the protein of HDL and plays a critical role in maintaining the integrity of HDL particles. Individuals with a profound deficiency of apo AI also lack HDL. Apo AI also activates the enzyme lecithin:cholesterol acyltransferase (LCAT), which esterifies free cholesterol in plasma. Plasma levels of HDL cholesterol and apo AI are inversely related to risk for CHD, and some patients with apo AI deficiency develop early, severe atherosclerosis. Transgenic mice overexpressing human apo AI are resistant to atherosclerosis. Apo AII is the second most abundant apoprotein in HDL, and its function has not been determined; transgenic mice that overexpress apo AII have high plasma levels of both HDL cholesterol and triglycerides and may be susceptible to atherosclerosis. Apo AII knockout mice have low levels of HDL, indicating that apo AII is also necessary for the integrity of HDL particles. Apo AIV, a minor component of HDL and chylomicrons, may play a role in the activation of LCAT.

Apoprotein(a), a large glycoprotein that shares a high degree of sequence homology with the plasma zymogen plasminogen, is made by hepatocytes and is secreted into plasma where it forms a covalent linkage with the apo B100 of LDL to form lipoprotein(a). The physiologic role of lipoprotein(a) is not known, but elevated levels are associated with an increased risk for atherosclerosis.

LIPOPROTEIN METABOLISM LPL is synthesized in fat and muscle, secreted into the interstitial space, transported across endothelial cells, and binds to proteoglycans on the luminal surfaces in the adjacent capillary beds. LPL mediates the hydrolysis of the triglycerides of chylomicrons and VLDL to generate free fatty acids

Table 341-2

Characteristics of the Major Apolipoproteins

Apolipoprotein	Molecular Mass, Da	Lipoproteins	Metabolic Functions
Apo AI	28,016	HDL, chylomicrons	Structural component of HDL; LCAT activator
Apo AII	17,414	HDL, chylomicrons	Unknown
Apo AIV	46,465	HDL, chylomicrons	Unknown: possibly facilitates transfer of other apos between HDL and chylomicrons
Apo B48	264,000	Chylomicrons	Necessary for assembly and secretion of chylomicrons from the small intestine
Apo B100	540,000	VLDL, IDL, LDL	Necessary for assembly and secretion of VLDL from the liver; structural protein of VLDL, IDL, LDL; ligand for LDL receptor
Apo CI	6630	Chylomicrons, VLDL, IDL, HDL	May inhibit hepatic uptake of chylomicron and VLDL remnants
Apo CII	8900	Chylomicrons, VLDL, IDL, HDL	Activator of lipoprotein lipase
Apo CIII	8800	Chylomicrons, VLDL, IDL, HDL	Inhibitor of lipoprotein lipase: may inhibit hepatic uptake of chylomicron and VLDL remnants
Apo E	34,145	Chylomicrons, VLDL, IDL, HDL	Ligand for binding of several lipoproteins to the LDL receptor, to LRP, and possibly to a separate hepatic apo E receptor

and glycerol. The free fatty acids diffuse into adjacent tissues to be burned for energy or stored as fat. Most circulating LPL is associated with LDL. Insulin stimulates the synthesis and secretion of LPL, and reduced LPL activity in diabetes mellitus can lead to impaired triglyceride clearance. Homozygotes for mutations that impair LPL have severe hypertriglyceridemia that is usually manifested in childhood (type I hyperlipidemia), and heterozygotes for LPL defects have mild to moderate fasting hypertriglyceridemia but may have marked hypertriglyceridemia after consuming a high-fat meal. LPL is also expressed in macrophages, including cholesteryl ester-laden macrophages (foam cells) in atherosclerotic lesions. In this setting, secreted LPL may associate with LDL, causing retention of the lipoprotein in the subendothelial space.

Hepatic triglyceride lipase (HTGL), a member of a family of enzymes that includes LPL and pancreatic lipase, is synthesized in the liver and interacts with lipoproteins in hepatic sinusoids. HTGL can remove triglycerides from VLDL remnants (IDL), thus promoting the conversion of VLDL to LDL, and may also play a role in the clearance of chylomicron remnants and in the conversion of HDL₂ to HDL₃ in the liver by hydrolyzing the triglyceride and phospholipid in HDL (see below). Severe hypertriglyceridemia in individuals with genetic deficiency of HTGL is due to accumulation of chylomicron and VLDL remnants in plasma. In contrast to most patients with hypertriglyceridemia, however, subjects with HTGL deficiency have normal levels of HDL.

LCAT is synthesized in the liver and secreted into plasma where it is bound predominantly to HDL. LCAT mediates the transfer of linoleate from lecithin to free cholesterol on the surface of HDL to form cholesteryl esters that are then transferred to VLDL and eventually LDL. Apo AI is a cofactor for esterification of free cholesterol by LCAT.

Cholesteryl ester transfer protein (CETP) is synthesized primarily in the liver and circulates in plasma in association with HDL. CETP mediates the exchange of cholesteryl esters from HDL with triglyceride from chylomicrons or VLDL. LDL cholesteryl ester can also be exchanged with triglyceride from chylomicrons and VLDL, leading to small, dense LDL. Individuals who are homozygotes for mutations in the CETP gene have marked elevations of HDL cholesterol and apo AI, and heterozygotes for these mutations have slight elevations of HDL, indicating that CETP plays an important role in the removal of cholesteryl esters from HDL.

TRANSPORT OF EXOGENOUS (DIETARY) LIPIDS

Exogenous lipid transport in chylomicrons and chylomicron remnants is depicted in Fig. 341-1A. In western societies, where individuals ordinarily consume 50 to 100 g of fat and 0.5 g of cholesterol during three or four meals, transport of dietary fats is essentially continual. Normolipidemic individuals dispose of most dietary fat in the bloodstream within 8 h of the last meal, but some individuals with dyslipidemia, particularly those with elevated fasting levels of VLDL triglyceride, have measurable levels of intestinally derived lipoproteins in the circulation as long as 24 h after the last meal.

In the intestinal mucosa dietary triglyceride and cholesterol are incorporated into the core of nascent chylomicrons. The surface coat of the chylomicron is composed of phospholipid, free cholesterol, apo B48, apo AI, apo AII, and apo AIV. The chylomicron, essentially a fat droplet containing 80 to 95 percent triglycerides, is secreted into lacteals and transported to the circulation via the thoracic duct. In the plasma, apo C proteins are transferred to the chylomicron from HDL. Apo CII is required for hydrolysis of triglycerides by LPL on capillary endothelial cells in fat and muscle, and apo CIII may modulate core triglyceride hydrolysis by regulating LPL activity. The addition of apo E allows the chylomicron remnant to bind to hepatic LDL receptors and/or LRP after the triglyceride core has been hydrolyzed and after apo CII and apo CIII have recirculated back to HDL. As a consequence, dietary triglyceride is delivered to adipocytes and muscle cells as fatty acids, and dietary cholesterol is taken up by the liver where it can be used for bile acid formation, incorporated into membranes, resecreted

as lipoprotein cholesterol back into the circulation, or excreted as cholesterol into bile. Dietary cholesterol also regulates endogenous hepatic cholesterol synthesis.

Abnormal transport and metabolism of chylomicrons may predispose to atherosclerosis, and postprandial hyperlipidemia may be a risk

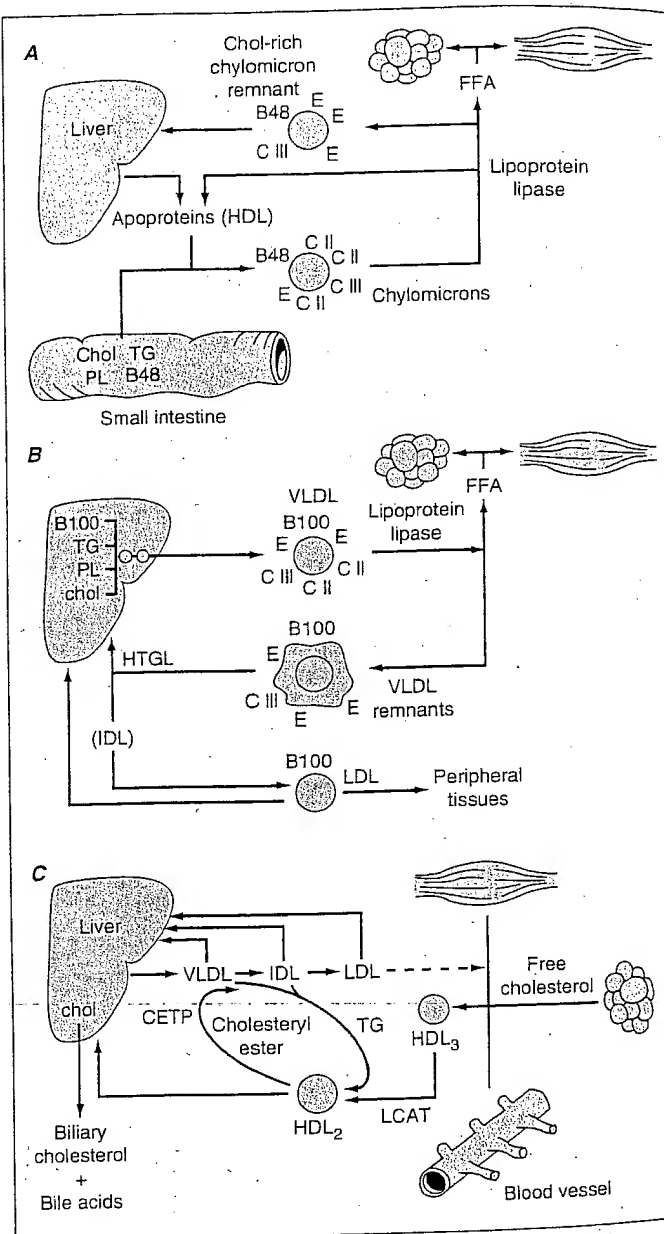


FIGURE 341-1 A. Transport of endogenous hepatic lipids via VLDL, IDL, and LDL. Note the relative and absolute changes in apoproteins, other than apo B100, as VLDL is converted to IDL and LDL. The sites of action of the two lipases, LPL and HTGL, are denoted as well, although the role of HTGL has not been completely defined. B. A schematic depiction of the transport of exogenously derived lipids from the intestine to peripheral tissues and liver via the chylomicron system. The cyclic movement of several apoproteins between HDL and chylomicrons is represented also. C. Simplified representation of HDL metabolism and the role of HDL in reverse cholesterol transport. Free cholesterol is accepted from peripheral tissues by HDL₃ and, after esterification, may be transferred to apo B100 lipoproteins. Cholesteryl ester also may be delivered to the liver by HDL itself. The significance of each of the three possible transport systems for cholesterol in overall reverse cholesterol transport is unknown. CETP, cholesteryl ester transfer protein; FFA, free fatty acids; HDL, high-density lipoprotein; HTGL, hepatic triglyceride lipase; IDL, intermediate-density lipoprotein; LDL, low-density lipoprotein; LPL, lipoprotein lipase; PL, phospholipase; TG, triglyceride; VLDL, very low density lipoprotein. [From HN Ginsberg. *Endocrinol Metab Clin North Am* 19(2):211, 1990.]

factor for CHD. Chylomicrons and their remnants can be taken up by cells of the vessel wall, including monocyte-derived macrophages that migrate into the vessel wall from plasma. Cholesteryl ester accumulation by these macrophages transforms them into foam cells, the earliest cellular lesion of the atherosclerotic plaque. If the postprandial levels of chylomicrons or their remnants are elevated or if their removal from plasma is prolonged, cholesterol delivery to the artery wall may be increased.

TRANSPORT OF ENDOGENOUS LIPIDS The endogenous lipid transport system, which conveys lipids from the liver to peripheral tissues and from peripheral tissues back to the liver, can be separated into two subsystems: the apo B-100 lipoprotein system (VLDL, IDL, and LDL) and the apo AI lipoprotein system (HDL).

The apo B100 Lipoprotein System (See Fig. 341-1B) In the liver, triglycerides are made from fatty acids that are either taken up from plasma or synthesized de novo within the liver. Cholesterol can also be synthesized by the liver or delivered to the liver via chylomicron remnants. These core lipids are packaged together with apo B100 and phospholipids into VLDL and secreted into plasma where apos CI, CII, CIII, and E are added to the VLDL particles. Triglycerides make up the bulk of the VLDL (55 to 80 percent by weight), and the size of the VLDL is determined by the amount of triglyceride available. Hence, very large triglyceride-rich VLDL is secreted in situations where excess triglycerides are synthesized, such as in states of caloric excess, in diabetes mellitus, and with alcohol consumption. Small VLDL is secreted when fewer triglycerides are available. Although VLDL is normally the principal hepatic lipoprotein secreted by most individuals, VLDL and cholesteryl ester-enriched IDL and/or LDL-like particles may be secreted by the liver in individuals with combined hyperlipidemia (see below).

In the plasma, VLDL interacts with LPL, and as the triglycerides are hydrolyzed, VLDL particles become smaller and more dense and are converted to VLDL remnants (IDL). In contrast to chylomicron remnants, VLDL remnants can either enter the liver or give rise to LDL. Larger VLDL particles carry more triglycerides and are likely to be removed directly from plasma without being converted to LDL; apo E in the VLDL remnants is the ligand that binds the remnants to the LDL receptor for removal from the plasma. Smaller, more dense VLDL particles are efficiently converted to LDL, and apo E and HTGL play important roles in this process. Individuals with deficiency of either apo E2 or HTGL accumulate IDL in plasma. Apo B100 is the only protein remaining on the surface of the LDL particle.

The half-life of LDL in plasma is determined principally by the availability (or "activity") of LDL receptors. Most plasma LDL is taken up by the liver, and the remainder is delivered to peripheral tissues, including the adrenals and gonads, which utilize cholesterol as a precursor for steroid hormone synthesis. The adrenals have the highest concentration of LDL receptors per cell in the body. Overall, about 70 to 80 percent of LDL catabolism occurs via LDL receptors, and the remainder is removed by fluid endocytosis and possibly by other receptors.

The LDL receptor, a glycoprotein with a molecular mass of approximately 160 kDa, is present on the surfaces of nearly all cells in the body. Goldstein and Brown characterized the molecular genetics and cell biology of the LDL receptor and defined its role in cholesterol metabolism by showing that cholesterol delivered to the cytoplasm by LDL regulates both the rate of cholesterol synthesis in the liver and the number of LDL receptors on the surface of hepatocytes. These feedback mechanisms allow cells to maintain cholesterol homeostasis. While the LDL receptor is a major factor in determining plasma LDL cholesterol levels, the rates of entry of VLDL into plasma and the efficiency with which VLDL is converted to LDL also influence steady-state LDL concentrations in plasma.

Increased levels of plasma LDL cholesterol and apo B100 are risk factors for atherosclerosis. Normal LDL does not cause foam cell formation when incubated with cultured macrophages or smooth-muscle cells, but when LDL undergoes lipid peroxidation it becomes a ligand for an alternative, scavenger receptor pathway. Scavenger receptors are present on endothelial cells and macrophages, and uptake

of modified (oxidized) lipoproteins by these receptors in macrophages results in formation of cholesterol-laden foam cells. In addition to inducing foam cell formation, oxidized LDL acts in the vessel wall to stimulate the secretion of cytokines and growth factors by endothelial cells, smooth-muscle cells, and monocyte-derived macrophages. The consequence is recruitment of more monocytes to the lesion and proliferation of smooth-muscle cells, which synthesize and secrete increased amounts of extracellular matrix, such as collagen. The critical role of LDL in atherosclerosis has been confirmed in genetically altered mice. Although mice are normally resistant to atherosclerosis, increased plasma levels of remnant lipoproteins or LDL lead to atherosclerosis in this species.

The role of VLDL in atherogenesis is uncertain. The major reason for this uncertainty derives from the inverse relationship between elevated levels of triglyceride-rich lipoproteins and reduced levels of the antiatherogenic HDL cholesterol, and it is possible that hypertriglyceridemia may not be directly atherogenic but the surrogate of other lipoprotein abnormalities. Hence, if postprandial hyperlipidemia is a risk factor for CHD, individuals who have normal fasting plasma triglyceride levels but develop postprandial hypertriglyceridemia after consumption of a fat load would be misclassified as normal in studies in which only fasting blood samples are analyzed. It is clear that cholesteryl ester-enriched VLDL, isolated from cholesterol-fed animals, can be taken up by receptors on macrophages and smooth-muscle cells and cause foam cell formation. These cholesteryl ester-rich VLDL are enriched in apo E and are probably representative of VLDL remnants. Thus, the risk of atherosclerosis from hypertriglyceridemia and elevated VLDL levels may be determined by the level of cholesteryl ester-enriched VLDL remnants within the plasma VLDL. The atherogenic potential of IDL is probably similar to that of VLDL remnants.

Apo AI-Containing Lipoproteins (See Fig. 341-1C) In contrast to atherogenic apo B lipoproteins, the apo AI-containing HDL appear to be antiatherogenic. In fact, in some studies, HDL cholesterol levels are as strong an indicator of protection from CHD as LDL cholesterol levels are an indicator of risk. Although a great deal is known about the HDL transport system, the mechanism by which these lipoproteins protect against atherosclerosis is poorly defined.

HDL particles are formed in plasma from the coalescence of individual phospholipid-apolipoprotein complexes. Apo AI appears to be the crucial, structural apolipoprotein for HDL, and apo AI/phospholipid complexes probably fuse with other phospholipid vesicles containing apo AII and apo AIV to form the various types of HDL. The C apoproteins can be added to HDL after their secretion as phospholipid complexes or by transfer from triglyceride-rich lipoproteins. These small, cholesterol-poor nascent HDL particles are heterogeneous in size and content and are referred to as HDL₂. Free cholesterol is transferred from cell membranes to HDL₂ and converted by LCAT to cholesteryl ester, which moves into the core of the particle. Formation of cholesteryl ester increases the capacity of the HDL₂ to accept more free cholesterol and enlarge to form the more buoyant class of HDL particles termed HDL₃. HDL₂ can be metabolized by two pathways: (1) cholesteryl esters can be transferred from HDL₂ to apo B lipoproteins or cells, or (2) the entire HDL₂ particle can be removed from plasma. The transfer of cholesteryl ester from HDL to triglyceride-rich, apo B lipoproteins (chylomicrons and VLDL in the fed and fasted states, respectively) is mediated by CETP. Triglyceride is transferred to HDL in this process and is a substrate for lipolysis by LPL and/or HTGL. As a result, HDL₂ is converted back into HDL₃. HDL-mediated reverse cholesterol transport (from peripheral tissues to the liver) is thought to be the primary mechanism by which HDL protects against atherosclerosis. When the apo B lipoproteins are removed by the liver, reverse cholesterol transfer is complete. HDL cholesteryl ester may also be transferred selectively to cells via interaction of HDL with cell membranes. Alternatively, the subset of HDL particles that contains apo E can be taken up in toto via LDL receptors or LRP.